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Published in:
Journal of Diabetes and its Complications

DOI:
[10.1016/j.jdiacomp.2018.09.005](https://doi.org/10.1016/j.jdiacomp.2018.09.005)

Publication date:
2018

Document version
Publisher's PDF, also known as Version of record

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Citation for published version (APA):
Chertow, G. M., Appel, G. B., Block, G. A., Chin, M. P., Coyne, D. W., Goldsberry, A., Kalantar-Zadeh, K., Meyer, C. J., Molitch, M. E., Pergola, P. E., Raskin, P., Silva, A. L., Spinowitz, B., Sprague, S. M., & Rossing, P. (2018). Effects of bardoxolone methyl on body weight, waist circumference and glycemic control in obese patients with type 2 diabetes mellitus and stage 4 chronic kidney disease. *Journal of Diabetes and its Complications*, 32(12), 1113-1117. <https://doi.org/10.1016/j.jdiacomp.2018.09.005>



Effects of bardoxolone methyl on body weight, waist circumference and glycemic control in obese patients with type 2 diabetes mellitus and stage 4 chronic kidney disease

Glenn M. Chertow^a, Gerald B. Appel^b, Geoffrey A. Block^c, Melanie P. Chin^d, Daniel W. Coyne^e, Angie Goldsberry^d, Kamyar Kalantar-Zadeh^f, Colin J. Meyer^d, Mark E. Molitch^g, Pablo E. Pergola^h, Philip Raskinⁱ, Arnold L. Silva^j, Bruce Spinowitz^k, Stuart M. Sprague^l, Peter Rossing^{m,*}

^a Stanford University School of Medicine, Palo Alto, CA 94304, United States

^b Columbia University Medical Center, Glomerular Kidney Disease Center, New York, NY 10032, United States

^c Denver Nephrology, Denver, CO 80230, United States

^d Reata Pharmaceuticals, Product Development, Irving, TX 75063, United States

^e Washington University, Division of Nephrology, St. Louis, MO 63110, United States

^f University of California, Irvine, Orange, CA 92688, United States

^g Northwestern University, Feinberg School of Medicine, Chicago, IL 60611, United States

^h Renal Associates PA, San Antonio, TX 78270, United States

ⁱ University of Texas, Southwestern Medical Center, Division of Endocrinology, Dallas, TX 75390, United States

^j Boise Kidney and Hypertension Institute, Meridian, ID 83642, United States

^k New York Presbyterian Queens, Flushing, NY 11355, United States

^l Northshore Medical University Health System – University of Chicago, Evanston, IL 60201, United States

^m Steno Diabetes Center Copenhagen, University of Copenhagen, Copenhagen, DK-2820, Gentofte, Denmark

Role of funding source: The study sponsor, Reata Pharmaceuticals, played an active role in trial design, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication. The corresponding author had full access to all data from the trial and had final responsibility for the decision to submit for publication.

Disclosure Information: GMC reports personal fees from Reata Pharmaceuticals, during the conduct of the study; personal fees from Akebia, AMAG, Ardelyx, Astra Zeneca, Gilead, Keryx, Bayer, Bristol-Myers Squibb, Otsuka, and ReCor; grants and personal fees from Amgen, other from Durect, Outset Medical, Physiowave, and Puracath Medical, outside the submitted work. GBA has research grants from Regulus, BM Squibb, EMD Serono, Alexion and Reata, a speaker for Genentech and Sanofi-Genzyme and a consultant for Alexion, Achillion, Ionis, Genentech, Mallinkrodt, Pfizer, Merck, Roche, Bristol-Myers Squibb, Up-to-Date, Amgen, Genzyme-Sanofi, EMD Serono, Regulus, and Reata. He has no major stock holdings or ownerships. GAB reports personal fees and non-financial support from Akebia, Amgen, Kirin, Reata, OPKO and ONO, personal fees from Daiichi-Sankyo, grants, personal fees and non-financial support from Keryx, personal fees and other from Ardelyx, outside the submitted work. MC and AG are employees of Reata Pharmaceuticals. DWC reports grants from Reata, during the conduct of the study and personal fees from Reata, outside the submitted work. KKZ reports personal fees from Abbott, Abbvie, Alexion, Amgen, Astra-Zeneca, Aveo, Chugai, Fresenius Medical Services, Genentech, Haymarket, Hospira, Kabi, Keryx, Novartis, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Vifor, ZS-Pharma, UpToDate, Baxter, Dr Schaefer, grants and personal fees from Shire, and other from DaVita and National Institutes of Health, outside the submitted work. CJM is an employee of Reata Pharmaceuticals. In addition, Dr. Meyer has a patent, Methods of Treating Obesity Using Antioxidant Inflammation Modulators (Pending in U.S. and a number of ex-US territories, granted in certain ex-US countries including Australia and Japan), licensed to AbbVie and Kyowa Hakko Kirin. MEM reports grants from Reata during the conduct of the study; grants and personal fees from Novartis, grants from Novo Nordisk, grants from Bayer, grants and personal fees from Janssen, personal fees from Merck, personal fees from Pfizer, outside the submitted work. PEP reports personal fees from Reata Pharmaceuticals, Akebia Therapeutics, ExThera Medical, Keryx Biopharmaceuticals, Astra-Zeneca, Gilead Sciences, Tricida Inc., Alnylam Pharmaceuticals, outside the submitted work; as the principal investigator for many pharmaceutical companies, his institution has received research support. PRA has been a consultant to Reata Pharmaceuticals. ALS reports grants from Reata Pharmaceuticals, during the conduct of the study. BSS has nothing to disclose. SMS reports grants from Reata Pharmaceuticals, during the conduct of the study. PR reports grants, and personal fees from Novo Nordisk, and Astra Zeneca, personal fees from Astellas, Boehringer Ingelheim, Bayer, and Eli Lilly. All fees are given to his institution.

* Corresponding author.

E-mail addresses: gchertow@stanford.edu (G.M. Chertow), GBA2@cumc.columbia.edu (G.B. Appel), gablock@dnresearch.org (G.A. Block), melanie.chin@reatapharma.com (M.P. Chin), dcoyne@wustl.edu (D.W. Coyne), angie.goldsberry@reatapharma.com (A. Goldsberry), kkz@uci.edu (K. Kalantar-Zadeh), colin.meyer@reatapharma.com (C.J. Meyer), molitch@northwestern.edu (M.E. Molitch), ppergola@raparesearch.com (P.E. Pergola), Philip.Raskin@UTSouthwestern.edu (P. Raskin), asilva@boisekidney.com (A.L. Silva), bss9001@nyp.org (B. Spinowitz), peter.rossing@regionh.dk (P. Rossing).

ARTICLE INFO

Article history:

Received 30 July 2018

Received in revised form 4 September 2018

Accepted 9 September 2018

Available online 13 September 2018

Keywords:

Bardoxolone methyl

Chronic kidney disease

Obesity

Metabolic effects

HbA_{1c}

Randomized clinical trial

ABSTRACT

Aims: Obesity is associated with progression of chronic kidney disease (CKD). Treatment with bardoxolone methyl in a multinational phase 3 trial, Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes (BEACON), resulted in increases in estimated glomerular filtration rate (eGFR) with concurrent reductions in body weight. We performed post-hoc analyses to further characterize reductions in body weight with bardoxolone methyl. **Methods:** Eligible patients with type 2 diabetes (T2DM) and CKD stage 4 (eGFR 15 to <30 mL/min/1.73 m²) were randomized 1:1 to receive once-daily oral dose of bardoxolone methyl (20 mg) or placebo.

Results: BEACON enrolled 2185 patients. Patients randomized to bardoxolone methyl experienced significant reductions in body weight from baseline relative to patients randomized to placebo (−5.7 kg; 95% CI: −6.0 to −5.3 kg; $p < 0.001$). In patients randomized to bardoxolone methyl, rate and magnitude of body weight loss were proportional to baseline BMI. Bardoxolone methyl resulted in significant reductions in waist circumference and improved glycemic control.

Conclusions: Bardoxolone methyl resulted in significant weight loss in a generally obese patient population with T2DM and stage 4 CKD, with the magnitude and rate dependent on baseline BMI.

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1. Introduction

Obesity increases the risk for type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease, as well as progressive chronic kidney disease.^{1,2} Obesity is characterized by changes in adipose tissue including the deposition of fat, enlargement of adipocytes, and a pro-inflammatory phenotype that leads to the development of insulin resistance and metabolic syndrome.^{3–5}

Bardoxolone methyl and related analogs have been shown to improve glycemic control, decrease lipid accumulation, and reduce inflammation in multiple animal models of diabetes and obesity,^{6–9} while also improving kidney function and preventing structural injury in models of kidney disease.^{10–13} Through activation of nuclear factor erythroid-derived 2-related factor 2 (Nrf2) and inhibition of nuclear factor kappa-light-chain-enhancer of activated B-cells (NF- κ B), bardoxolone methyl up-regulates the antioxidant response and suppresses pro-inflammatory signaling to reduce oxidative stress and inflammation and promote mitochondrial function.^{14,15}

Bardoxolone methyl has also been studied in at least seven clinical trials enrolling approximately 2600 patients with type 2 diabetes (T2DM) and CKD. Improvements in kidney function, assessed using measured inulin clearance, measured creatinine clearance, and estimated glomerular filtration rate (eGFR), have been observed consistently with bardoxolone methyl treatment in several clinical trials.^{16–19} The largest of these was a multinational, randomized, double-blind, placebo-controlled phase 3 outcomes trial, which enrolled 2185 patients with T2DM and CKD stage 4 [Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes: The Occurrence of Renal Events (BEACON)].¹⁸ The BEACON trial was terminated early because of safety concerns, largely driven by a significant increase in heart failure events within the first four weeks of exposure. Patients randomized to bardoxolone methyl experienced significantly improved kidney function. Lower serum creatinine concentrations (corresponding to higher eGFRs), along with lower serum concentrations of urea nitrogen, uric acid, and phosphorus were observed. In concert with improved kidney function, reductions in body weight were also observed in bardoxolone methyl-treated patients. Given that serum creatinine concentration depends on its clearance as well as its generation as a function of skeletal muscle mass²⁰ and to address the question as to whether the observed decrease in serum creatinine was related to improved GFR versus a loss of muscle mass, we performed post-hoc analyses to further characterize reductions in body weight induced by bardoxolone methyl treatment.

2. Materials and methods

2.1. Study design

The BEACON trial (NCT01351675) was a phase 3, randomized, double-blind, parallel-group, international, multicenter trial of once-daily administration of bardoxolone methyl (20 mg), as compared

with placebo. Previous publications describe the BEACON trial design in detail.^{18,21} The study protocol was approved by Institutional Review Boards or Ethics Committees at participating sites and all patients provided written informed consent.

BEACON enrolled adults with type 2 diabetes mellitus and stage 4 CKD, corresponding to an eGFR of 15 to <30 mL/min/1.73 m². Patients were randomized 1:1 to once-daily administration of bardoxolone methyl or placebo. Patients received background conventional therapy that included inhibitors of the renin–angiotensin–aldosterone system, insulin or other hypoglycemic agents, and, when appropriate, other cardiovascular medications.

Estimated GFR was calculated using serum creatinine and the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation. Estimated GFR and vital signs (including body weight and Quetelet's (body mass) index (BMI)) were assessed every 4 weeks through Week 12, followed by assessments every 8 weeks thereafter. Waist circumference and hemoglobin A_{1c} (HbA_{1c}) were assessed every 24 weeks. A subset of the patients ($n = 174$, 8%) consented to additional 24-hour urine collections at baseline and Week 4; to assess whether the weight loss was derived from muscle mass or adipose tissue, we examined changes in urinary creatinine excretion over 24 h.

The primary composite endpoint of the trial was the time-to-first event in the composite outcome defined as end-stage renal disease (ESRD; need for maintenance dialysis, kidney transplantation, or renal death) or cardiovascular death. Secondary efficacy outcomes included the change in eGFR, time-to-first hospitalization for heart failure or death due to heart failure, and time-to-first event of a composite consisting of non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, or cardiovascular death.

2.2. Statistical analysis

We analyzed the BEACON population using summary statistics to compare changes in body weight, waist circumference, and HbA_{1c} in patients randomized to bardoxolone methyl or placebo in accordance with the intention-to-treat principle. One-sample (paired) *t*-tests were used for comparing mean changes to zero and two-sample *t*-tests were used to compare the difference in means between bardoxolone methyl and placebo groups. Longitudinal analyses of body weight were also used to compare mean changes in body weight between the bardoxolone methyl and placebo groups. As previously described, mixed-effects regression used post-baseline body weight as the response variable; treatment group, time, the interaction of treatment group with time, interaction of baseline body weight with time; and continuous covariates (body weight at baseline, baseline eGFR and urinary albumin-to-creatinine ratio).¹⁸

3. Results

As previously published, from June 2011 through September 2012, a total of 2185 patients were randomized to receiving either bardoxolone

methyl ($n = 1088$) or placebo ($n = 1097$).¹⁸ Previous publications also describe the demographics and baseline characteristics of the patients randomized to bardoxolone methyl versus those randomized to placebo in BEACON,²² which are summarized in Table 1, along with characteristics of the 174 patients who consented to 24-hour urine collections. The demographics and baseline characteristics for the subset of patients that consented to additional 24-hour urine collections were similar to that of the entire BEACON population and between patients randomized to bardoxolone methyl or placebo.

3.1. Weight

The majority of patients enrolled in BEACON were overweight or obese; 93% of patients had BMI ≥ 25.0 kg/m² at baseline. The mean BMI and body weights at baseline were 33.7 ± 7.1 kg/m² and 95.1 ± 22.0 kg for patients randomized to bardoxolone methyl ($n = 1088$), and 33.9 ± 7.2 kg/m² and 95.3 ± 21.1 kg for patients randomized to placebo ($n = 1097$). As previously reported, patients randomized to bardoxolone methyl experienced a significant reduction in body weight compared to placebo (-5.7 kg [95% CI: -6.0 to -5.3 kg]; $p < 0.001$).¹⁸

In patients randomized to bardoxolone methyl, the rate and magnitude of body weight loss were proportional to baseline BMI (Fig. 1). Body weight plateaued at 32 weeks in patients within the World Health Organization (WHO) lean and normal BMI groups at baseline (18.5 to 24.9 kg/m²), while it continued to decline in patients who were overweight (25.0 to 29.9 kg/m²) or obese (≥ 30 kg/m²) at baseline.

3.2. Waist circumference

Bardoxolone methyl treatment significantly decreased waist circumference relative to baseline and relative to placebo at Weeks 24 and 48 ($p < 0.01$; Fig. 2, panel A). Bardoxolone methyl-treated patients had mean (\pm SD) decreases in waist circumference of -4.1 ± 8.0 cm ($n = 622$) at Week 24 and -6.5 ± 9.3 cm ($n = 239$) at Week 48. In contrast, placebo-treated patients experienced minimal to no change in waist circumference at Week 24 and Week 48 (mean \pm SD -0.4 ± 8.4 ($n = 717$) and 0.0 ± 8.6 ($n = 280$) at Weeks 24 and 48, respectively). Similar to changes in body weight, the magnitude of reductions in waist circumference with bardoxolone methyl treatment was proportional to baseline BMI; obese patients experienced more pronounced reductions in waist circumference compared with patients who were not obese (Fig. 2, panel B).

3.3. 24-Hour urinary excretion

As seen in Table 1, the mean baseline BMI and body weight for the subset of patients who consented to additional 24-hour urine collections

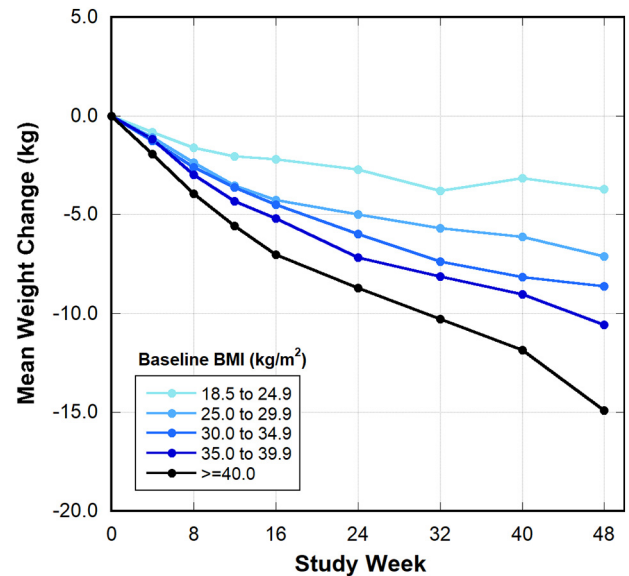


Fig. 1. Changes from baseline in body weight with bardoxolone methyl by baseline BMI. Mean changes from baseline in body weight (kg) for patients randomized to bardoxolone methyl stratified by baseline BMI categories using World Health Organization (WHO) classifications: Underweight (< 18.5 kg/m²): $n = 0$ (0%); normal weight (18.5 to 24.9 kg/m²): $n = 78$ (7%); overweight (25.0 to 29.9 kg/m²): $n = 269$ (24%); class I obesity (30.0 to 34.9 kg/m²): $n = 334$ (31%); class II obesity (35.0 to 39.9 kg/m²): $n = 231$ (21%); class III obesity (≥ 40.0 kg/m²): $n = 175$ (16%).

were similar to that of the entire BEACON population. Accordingly, significant reductions in body weight were observed in patients randomized to bardoxolone methyl at Week 4 (mean \pm SD = -0.7 ± 2.0 kg; $p = 0.03$ for bardoxolone methyl versus placebo). Conversely, mean (\pm SD) 24-hour urinary creatinine excretion with bardoxolone methyl was unchanged from baseline at Week 4 (1134 ± 394 mg versus 1191 ± 339 mg at baseline; $n = 61$) and was not significantly different from changes with placebo (Table 2; $p = 0.33$).

3.4. Hemoglobin A_{1c}

Mean baseline HbA_{1c} was $7.15 \pm 1.27\%$ and $7.10 \pm 1.17\%$ for patients randomized to bardoxolone methyl and placebo, respectively. Bardoxolone methyl treatment significantly decreased HbA_{1c} relative to baseline at Week 24 (-0.12 ± 1.04 ; $p = 0.0033$) and at Week 48 ($-0.17 \pm 1.13\%$; $p = 0.026$; Table 3); between group differences were also statistically significant at Week 24 and Week 48 (-0.13 ± 1.01 , $p = 0.023$ and -0.25 ± 1.13 , $p = 0.014$, respectively), as HbA_{1c}

Table 1

Select demographics and baseline characteristics of BEACON patients.

	Intent-to-treat population		Patients with 24-hr urine collections	
	Placebo ($n = 1097$)	Bardoxolone methyl ($n = 1088$)	Placebo ($n = 87$)	Bardoxolone methyl ($n = 87$)
Age, yr (mean \pm SD)	68.2 \pm 9.4	68.9 \pm 9.7	67.2 \pm 10.3	67.8 \pm 10.4
Female (n , %)	472 (43)	462 (42)	42 (48)	37 (43)
Race (n , %)				
Caucasian	848 (77)	846 (78)	61 (70)	68 (78)
Black	176 (16)	185 (17)	14 (16)	11 (13)
Other	73 (7)	57 (5)	12 (14)	8 (9)
Weight, kg (mean \pm SD)	95.3 \pm 21.1	95.1 \pm 22.0	95.9 \pm 24.1	94.3 \pm 20.5
BMI, kg/m ² (mean \pm SD)	33.9 \pm 7.2	33.7 \pm 7.1	34.3 \pm 7.9	33.7 \pm 6.4
HbA _{1c} , % (mean \pm SD)	7.10 \pm 1.17	7.15 \pm 1.27	6.97 \pm 0.97	7.36 \pm 1.54
Serum creatinine, mg/dl (mean \pm SD)	2.7 \pm 0.6	2.7 \pm 0.6	2.8 (0.6)	2.7 (0.5)
eGFR, ml/min/1.73 m ² (mean \pm SD)	22.5 \pm 4.6	22.4 \pm 4.3	21.8 (4.2)	22.7 (4.3)
UACR, mg/g (geometric mean)	221	210	221	210
Insulin (n , %)	677 (62)	667 (61)	48 (55)	53 (61)

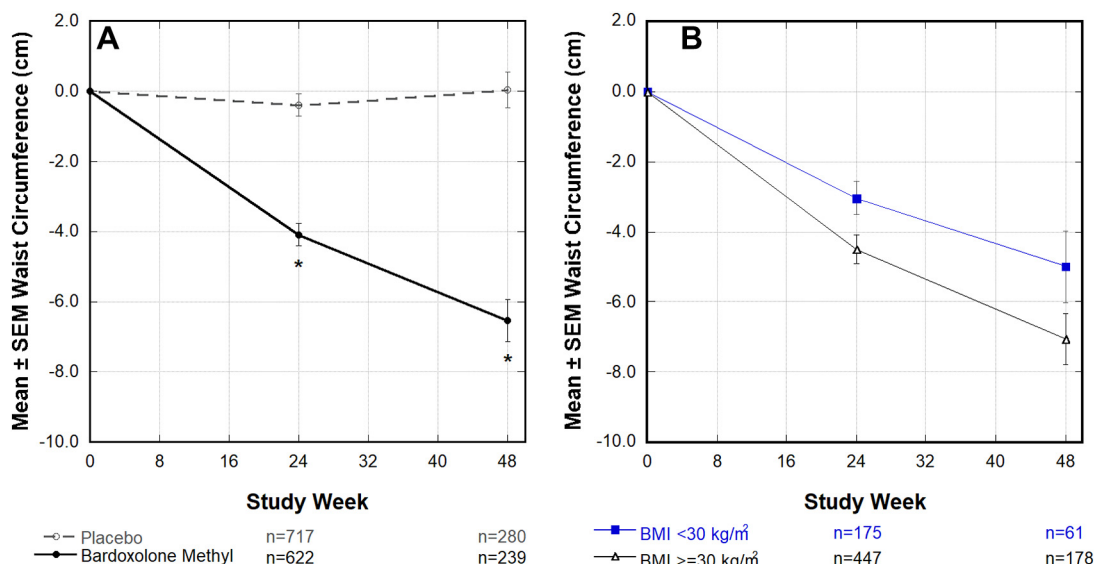


Fig. 2. Changes from baseline in waist circumference. Left. Mean changes (\pm SEM) from baseline in waist circumference (cm) for patients randomized to bardoxolone methyl or placebo in BEACON. * $p < 0.001$ versus placebo. Right. Mean changes (\pm SEM) from baseline in waist circumference for patients randomized to bardoxolone methyl stratified by non-obese baseline BMI ($< 30 \text{ kg/m}^2$) versus obese baseline BMI ($\geq 30 \text{ kg/m}^2$) categories.

values were unchanged in patients randomized to placebo. More importantly, reductions in HbA_{1c} induced by bardoxolone methyl were driven by results in patients with abnormal HbA_{1c} ($>7.0\%$) at baseline; mean changes in HbA_{1c} after 48 weeks of bardoxolone methyl treatment were $-0.53 \pm 1.47\%$ in patients with baseline $\text{HbA}_{1c} > 7.0\%$ (Table 3).

4. Discussion

Bardoxolone methyl treatment resulted in significant reductions in body weight in a generally overweight and obese patient population with T2DM and stage 4 CKD. The magnitude and rate of weight reductions were more pronounced in patients with higher baseline BMI. The loss in body weight was accompanied by a significant reduction in waist circumference, with declines proportional to both baseline body weight and BMI. Moreover, bardoxolone methyl significantly improved glycemic control with results driven by patients with HbA_{1c} above clinical practice guideline recommended targets at baseline. Finally, in a subset of patients who provided timed urine collections, there was no reduction in 24-hour urinary creatinine excretion, suggesting that the loss in body weight was not due to muscle wasting, but rather to loss of adipose tissue, findings consistent with the changes in waist circumference and glycemic control observed in the larger trial population. It is noteworthy that the BEACON trial protocol neither mandated nor recommended any particular diet, exercise or other lifestyle modifications that might account for the observed weight loss.

The trajectory and profile of increases in eGFR following treatment with bardoxolone methyl differ from that of the reductions in body weight; unlike mean changes from baseline in body weight, mean

increases in eGFR with bardoxolone methyl were apparent by Week 4 of treatment. In a Japanese trial, bardoxolone methyl significantly increased measured GFR, as assessed by inulin clearance, in patients with T2DM and stage 3 CKD after 16 weeks of treatment compared to placebo,¹⁹ demonstrating that bardoxolone methyl-mediated improvements in eGFR reflect true improvements in measured GFR.

Multiple studies in preclinical models of diabetes and obesity have demonstrated that bardoxolone methyl and its analogs reduce fat production and promote beta-oxidation of lipids to be used as fuel for energy production and reduced food intake.⁶ These effects are associated with improved glucose tolerance and insulin sensitivity, reduced body fat, preservation of muscle mass, and increased metabolism and energy expenditure.^{6,7,23} Moreover, bardoxolone methyl has also been shown to prevent hypothalamic inflammation, leptin resistance, and body weight gain in mice fed high-fat diets.²⁴ Although the mechanism of the weight loss associated with bardoxolone methyl treatment in humans is not fully understood, the prevention of leptin signaling impairments, maintenance of energy homeostasis, increased lipolysis of peripheral lipid stores, and improvements in glycemic control observed in preclinical studies may explain the reductions in body weight observed in patients with T2DM and CKD.

Strengths of this trial include a randomized design, a diverse patient population, and high clinical relevance to patients with T2DM and CKD. There was consistency of findings suggesting loss of adipose tissue rather than muscle mass across multiple parameters including body weight, waist circumference, 24-hour urinary creatinine excretion, and HbA_{1c} . While we hypothesized a beneficial effect on body weight and metabolism in bardoxolone methyl-treated patients, the trial was not designed to examine changes in body weight, waist circumference, and glycemic control; thus additional trials may be required to confirm these findings. Assessment of inflammatory markers in future studies may also elucidate how the anti-inflammatory effects of bardoxolone methyl are associated with the changes in body weight and other metabolic parameters.

While the effects on body weight and related parameters with bardoxolone methyl are generally considered beneficial in an obese population with T2DM and CKD, weight loss may be an undesirable effect in some patients. Subgroup analyses suggest that there was very limited loss of body weight in the small fraction of patients who were not overweight or obese. Moreover, the magnitude of weight reduction, trimming of waist circumference, and improvements in glycemic

Table 2
24-Hour urinary creatinine excretion over time and change from baseline.

Urinary creatinine (mg/24 h)	Placebo N = 65	Bardoxolone methyl N = 61
Baseline	1159 \pm 471	1191 \pm 339
Week 4	1155 \pm 457	1134 \pm 394
Change from Baseline	-4 \pm 327	-57 \pm 280

Data are mean values \pm SD and only include patients with baseline and Week 4 urinary creatinine values.

Table 3Change from baseline in hemoglobin A_{1c}.

	Observed HbA _{1c} (%)			Change from baseline (%)	
	Baseline	Week 24	Week 48	Week 24	Week 48
All patients					
Placebo ^a	7.10 ± 1.17 (n = 1097)	7.11 ± 1.29 (n = 721)	7.24 ± 1.44 (n = 275)	0.00 ± 0.99 (p = 0.92)	0.08 ± 1.12 (p = 0.24)
Bardoxolone methyl ^a	7.15 ± 1.27 (n = 1088)	6.96 ± 1.30 (n = 629)	6.90 ± 1.32 (n = 236)	−0.12 ± 1.04 (p = 0.0033)	−0.17 ± 1.13 (p = 0.026)
Difference between treatment groups ^b				−0.13 ± 1.01 (p = 0.023)	−0.25 ± 1.13 (p = 0.014)
Baseline HbA _{1c} > 7.0%					
Placebo ^a	8.10 ± 0.91 (n = 501)	7.90 ± 1.21 (n = 338)	8.07 ± 1.41 (n = 137)	−0.18 ± 1.14 (p = 0.0043)	0.00 ± 1.39 (p = 1.0)
Bardoxolone methyl ^a	8.22 ± 0.98 (n = 509)	7.76 ± 1.32 (n = 283)	7.74 ± 1.44 (n = 100)	−0.44 ± 1.29 (p < 0.001)	−0.53 ± 1.47 (p < 0.001)
Difference between treatment groups ^b				−0.26 ± 1.21 (p = 0.0086)	−0.53 ± 1.42 (p = 0.0051)
Baseline HbA _{1c} ≤ 7.0%					
Placebo ^a	6.25 ± 0.51 (n = 596)	6.42 ± 0.90 (n = 383)	6.41 ± 0.87 (n = 138)	0.16 ± 0.80 (p < 0.001)	0.16 ± 0.76 (p = 0.015)
Bardoxolone methyl ^a	6.21 ± 0.54 (n = 579)	6.31 ± 0.83 (n = 346)	6.28 ± 0.78 (n = 136)	0.14 ± 0.69 (p < 0.001)	0.10 ± 0.70 (p = 0.084)
Difference between treatment groups ^b				0.03 ± 0.75 (p = 0.60)	−0.05 ± 0.73 (p = 0.53)

Data are mean values ± SD.

^a p-Values comparing values at Week 24 or Week 48 to baseline values within each treatment group.^b p-Values comparing the difference in means between the bardoxolone methyl and placebo groups.

control in overweight and obese patients compare favorably to other interventions.

5. Conclusions

In summary, in patients with T2DM and stage 4 CKD, treatment with bardoxolone methyl results in significant loss of body weight, without evidence of muscle wasting. Reductions in waist circumference and improvements in glycemic control suggest generally favorably metabolic effects in overweight and obese persons. If the risk of symptomatic heart failure after treatment initiation can be mitigated by dose titration, dietary salt restriction or other strategies, bardoxolone methyl may prove to be an effective treatment for obesity in patients with T2DM.

Acknowledgements

We Acknowledge The Supportive Role Of All BEACON Investigators, Support Staff And Patients. We Thank Shobhana Natarajan, Phd., Of Reata Pharmaceuticals, For Assistance In Preparation Of The Manuscript.

Funding

The study sponsor, Reata Pharmaceuticals, played an active role in trial design, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

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